REMARKS

I. Status of the Claims

Claims 30, 31, 33, 38, and 39 are pending in the application. Claims 1-29, 32, and 34-37 have been canceled. Claims 30, 31, 33, 38, and 39 remain rejected. Applicants have amended claims 30 and 33 without prejudice or disclaimer and reserve the right to pursue any canceled subject matter in a divisional or continuation application.

Applicants have amended claims 30 and 33 to cancel the recitation of Y comprising "an amino acid sequence which is not derived from NS5B." Claims 30 and 33 have also been amended to recite "methionine residues in the amino acid sequence of X are replaced by selenomethionine residues." Support for this amendment is found in the specification, for example, at page 22, lines 17-19. Applicants have also amended claim 30 to replace "by binding to" with "interacts with said active site" to further clarify the criteria under which a test compound inhibits a HCV polymerase. Support for this amendment is found in the specification, for example, at page 12, lines 7-22. Applicants have also amended claim 30 to add a recitation of "and wherein said test compound interacts with a hydrophobic surface at the boundary domain between Thumb and Palm domains of said polypeptide derived from an NS5B HCV polymerase." Support for this amendment is found in the specification, for example, at page 281, lines 5-33. The Applicants have also amended claim 30 to more affirmatively describe the attributes of the test substance. No new matter has been added.

Applicants respectfully request entry of the above amendments as they place the

claims in condition for allowance, or reduce the number of issues for appeal. MPEP § 714.12.

II. Priority

The Office acknowledges Applicants' claim for foreign priority under 35 U.S.C. § 119 (a)-(d). Office Action, page 2. The Office then mischaracterizes the Applicants' benefit of priority by concluding "the instant application does not receive the priority benefit of [the two] foreign applications...." *Id.*, pages 2-3.

Applicants point out that under the provisions of 35 U.S.C. § 119, the instant application does receive the benefit of priority for all subject matter in common between the instant application and the two priority applications JP 11-188630, filed July 2, 1999 ("JP'630"), and JP 11-192488, filed July 7, 1999 ("JP'488"). The priority applications do disclose subject matter in common with the instant application.

III. Written Description Rejection

The Office has rejected claims 30, 31, and 38 under 35 U.S.C. § 112, first paragraph, as including new matter because "the newly added limitation 'polypeptide inhibits...by binding to said active and/or RNA binding cleft of said HCV polymerase' " is allegedly not found in the specification. Office Action, page 3. Applicants traverse the rejection.

In order to advance prosecution and without acquiescence, however, Applicants have amended claim 30 to recite as a step in the test, "interacts with said active site and/or RNA binding cleft". Support for this amendment is found in the specification at page 22, lines 17-19

Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Enablement Rejection

The Office has maintained the rejection of claims 30, 31, 33, 38, and 39 under 35 U.S.C. § 112, first paragraph, asserting that the specification, while enabling a use of a crystal structure of HCV polymerase using $NS5B_{570, 544, 536}$ and $_{531}$, does not reasonably provide enablement for all HCV polymerase." Office Action, page 4. Specifically, the Office alleges that the limitation recited in claims 30 and 33 of "Y...is not derived from NS5B" is not enabled by the specification. *Id.*, page 5. Applicants traverse the rejection for reasons of record.

However, in order to advance prosecution and without acquiescence, Applicants have amended claims 30 and 33 to cancel the recitation of Y comprising "an amino acid sequence which is not derived from NS5B." Applicants submit that the specification fully enables the claims as amended for reasons of record. Further, as noted above, the Office acknowledges that the specification is "enabling for a crystal structure of HCV polymerase using $NS5B_{570, 544, 536}$ and $_{531}$." Id., page 4.

Applicants therefore respectfully request entry of the amendment and reconsideration and withdrawal of the rejection.

V. Obviousness Rejections

Claims 30, 31, 33, 38 and 39 remain rejected under 35 U.S.C. § 103(a) as being obvious over Kim *et al.*, U.S. Patent 6,183,121 ("'Kim") in view of *In re Gulack*, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983) taken with Bressanelli *et al.* Proc. Natl. Acad. Sci. USA 96:13034-13039 (1999) ("Bressanelli"); and over Kim in view of *In*

re Gulack. Office Action, pages 4-15. Applicants traverse these rejections for reasons of record and as supplemented below.

The Office Erroneously Cites *Gulack* as Prior Art

In making the current obviousness rejections, the Office characterizes them as "Kim et al. (U.S. Patent 6,183,121 B1) in view of *In re Gulack*, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983) taken with Bressanelli et al. (1999)", and "Kim et al. (U.S. Patent 6,183,121 B1) in view of *In re Gulack*, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)." Office Action, pages 7 and 13, emphasis added. By stating the rejections in this manner, the Office has mischaracterized *Gulack* as a prior art reference.

MPEP § 706.02(j) states:

> 35 U.S.C. § 103 authorizes a rejection where, to meet the claim, it is necessary to modify a single reference or to combine it with one or more other references. After indicating that the rejection is under 35 U.S.C. 103, the examiner should set forth in the Office Action:
>
> (A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate, ...

The Office presents *Gulack* solely for the legal principles discussed therein. The Office is not relying upon *Gulack* for any factual technical teaching or suggestion. The factual technical teachings or suggestions of *Gulack* are not being modified or combined with Kim and Bressanelli. Thus, the Office is not relying upon *Gulack* as prior art. Accordingly, Applicants respectfully request that the Office remove *Gulack* from the recitation of the prior art being applied in the obviousness rejections.

Finally, Applicants reiterate their previous argument that the cited printed matter cases (such as *Gulack*) are not relevant to Applicants' claimed invention. The present

claims are drawn to methods of identifying HCV polymerase inhibitors by determining the "complementarity" of a test compound using three-dimensional structural coordinates. This invention is far from simple printed lines and characters.

Erroneous Reading of Kim

Applicants also respectfully point out that the Office has appeared to have misread Kim. In maintaining the rejection, the Office asserts:

> [O]ne of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement disclosed by Kim et al. for a method that uses molecular design techniques to identify, select and design chemical entities, including inhibitory compounds based on the 3-dimensional structure of a polymerase (Column 14, lines 27-38) and apply such method to the crystal structure for RNA-dependent RNA polymerase of hepatitis C virus as disclosed by Bressanelli et al.

Office Action, page 9, emphasis added. The Office continues by alleging that "[t]he polypeptide, NS3 helicase, of Kim et al. is a derivative of NS5B HCV polymerase (column 1, lines 46-67.)" *Id.*, emphasis added.

Applicants respectfully disagree because NS3 helicase is not a derivative of NS5B HCV polymerase. Kim clearly states that "[p]roteolytic processing of the HCV polyprotein by virally-encoded proteases generates several nonstructural (NS) proteins.... NS2..., NS5B..., and NS3...." Column 1, lines 47-67, emphasis added. This demonstrates that NS3 helicase and NS5B polymerase are separate and distinct HCV NS proteins, and that each is derived as distinct proteins by proteolytic processing from HCV polyprotein. Clearly, NS3 helicase is not a derivative of NS5B HCV polymerase as is erroneously asserted by the Office.

Similarly, the Office erroneously states that Kim discloses a method of designing chemical entities "including inhibitory compounds based on the 3-dimensional structure

of polymerase (Column 14, lines 27-38)..." Office Action, page 9. Column 14, lines 27-38, of Kim discloses design techniques that rely only upon structural coordinates from NS3 helicase. As discussed above, NS3 is not a derivative of NS5B HCV polymerase, and there is no evidence of record that NS3 helicase functions as a polymerase.

Applicants previously noted this erroneous assertion of the disclosure of the 3-dimensional structure of a "polymerase" in the response filed March 23, 2004, at page 13, and respectfully reiterates their request for a response.

The References Do Not Teach or Suggest All Recited Claim Limitations

Without aquiesence in the rejection, Applicants have amended claim 30 to recite "and wherein said test compound interacts with a hydrophobic surface at the boundary domain between Thumb and Palm domains of said polypeptide derived from an NS5B HCV polymerase." Neither of the references teach or suggest this aspect of the invention.

As set forth in the specification, by comparing the HCV polymerase activity of various-length NS5B polypeptides with the three-dimensional structural information of the present invention, the inventors thereby identified specific polypeptide positions and regions that can be a target for effective HCV polymerase inhibition. For example, the specification describes a test compound that strongly interacts with a hydrophobic surface at the boundary domain between Thumb and Palm domains of a polypeptide derived from an NS5B HCV polymerase. Page 281, line 5, to page 282, line 6. In particular, the inventors discovered that "the region at positions 545 to 552 and its partial fragment or a compound containing these fragments are particularly effective as

HCV polymerase inhibitors." Page 281, lines 14-16. Further analysis showed that "the region at positions 545 to 552 maintains hydrophobic interaction with the region comprising the hydrophobic surface existing in 'boundary site between Thumb and Palm domains'" and that polypeptide fragments at positions 545 to 552...strongly interact with said hydrophobic surface." Id, at lines 17-24. Further, "it was confirmed that the polypeptide region at positions 545 to 552 and its partial fragment or a compound containing these fragments are effective as HCV polymerase inhibitors." Id., lines 30-33. Therefore, a compound with a structure similar to the region can be an HCV polymerase inhibitor. Id., lines 8-10.

This claimed invention is neither taught nor suggested by the combination of references. Of course, Kim does not disclose the use of this boundary domain because it does not relate to polymerases. Furthermore, Bressanelli does not teach or suggest that HCV polymerase inhibitors interact effectively at a hydrophobic surface of a "boundary site between Thumb and Palm domains" of NS5B HCV polymerase.

Applicants respectfully request entry of the amendments and reconsideration and withdrawal of the rejection.

No Motivation to Combine the References

To further support its assertion, the Office points to Kim's discussion of "binding pockets" as evidence of motivation to combine the references. Office Action, page 9. Kim discloses that binding pockets "are of significant utility in fields such as drug discovery", that "many drugs exert...effects through association with the binding pockets", and "this information is valuable in designing potential inhibitors of the binding sites of biologically important targets." Col. 6, lines 16-29; and Office Action, page 9.

Tthis general discussion of the potential value of associations between drugs and "binding pockets" is merely a general overview of one theory underlying modern drug discovery. At most, Kim provides only the most general incentive to try to find molecules that associate with the binding pockets of any biologically important target. "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995). At best, it may have been obvious to try such a combination. However, obvious to try is not the standard. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); M.P.E.P. § 2145(X)(B). The only motivation to combine the references and derive the claimed invention comes from the Applicants' own specification, and this is clearly improper basis on which to rely.

No Reasonable Expectation of Success

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success of combining the cited references to arrive at the claimed invention. M.P.E.P. § 2143.

In response to Applicants' previous arguments that there is no indication that Kim's method for resolving HCV helicase binding pockets would be equally successful for resolving putative binding pockets for a HCV polymerase, the Office maintains the rejection. In support of its position the Office indicates that Kim discloses that "the polypeptide, NS3 helicase, is a derivative of NS5B HCV polymerase (column 1, lines 47-67)," and concludes:

> The disclosure cited above suggests that one of ordinary skill in the art at the time of the instant invention would have a reasonable expectation of success from combining the disclosure of Kim et al. and Bressanelli et al.

> in a method for identifying inhibitors of [sic] based on HCV helicase or HCV polymerase structure data.

Office Action, page 10. As discussed above, NS3 helicase is not a derivative of NS5B HCV polymerase. Therefore the evidence cannot support the Office's conclusion that there would be a reasonable expectation of success to combine Kim and Bressanelli in a method for identifying inhibitors based on HCV helicase or HCV polymerase structure data.

For any of the reasons above, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the amendment and remarks presented, Applicants submit that claims 30, 31, 33, and 38 and 39 are in condition for allowance and respectfully request entry of the amendments, and reconsideration and withdrawal of the rejections.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: September 14, 2004

By: _____
Charles D. Niebylski
Reg. No. 46,116